

# Altered Liver and Renal Serum Marker Enzymes in Alloxan Induced Diabetic Rats Treated with *Phyllanthus niruri*

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## Altered Liver and Renal Serum Marker Enzymes in Alloxan Induced Diabetic Rats Treated with *Phyllanthus niruri*

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### ABSTRACT

Extract of *Phyllanthus niruri* had antidiabetic effect. This is interesting to be investigated further remembering that the study of liver and kidney serum marker in diabetic rats has not been widely learned. Five groups of rats were used in this study, consisting of a group of healthy rats and four groups of diabetic rats. The four groups of diabetic rats, one group was no treat and the three other groups were treated with the extract of *Phyllanthus niruri* 1.35 mg / kg / day; 2.7 mg / kg bw / day and 5.4 mg / kg bw / day orally for 28 days. The result showed that the administration of *P. niruri* extract can reduce levels of AST, ALT, BUN and creatinine as normal in diabetic rats. This is probably due to its antioxidant activity, anti-inflammatory and antidiabetic activity. Hence the study reveal the therapeutic use of *P. niruri* extract on diabetes and its complications.

**KEYWORDS :** Diabetes mellitus, alloxan, *Phyllanthus niruri*, liver, kidney, serum marker

### INTRODUCTION

37 Diabetes is currently known as the most widely recognized cause for liver disease in the U.S.A. Liver disease is also an important cause of death in type 2 diabetes [1]. Almost the entire spectrum of liver disease seen in patients with type 2 diabetes mellitus, for example, abnormal liver enzymes, non-alcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure. Finally, the prevalence of diabetes in cirrhosis is 12.3 to 57% [2]. Impaired liver function can be used as indicator of target organ conditions associated with diabetes, such as glomerulopathy, retinopathy and neuropathy. Annual examination for liver disease might be accomplished by means of a simple biochemical analyte such as alanine aminotransferase [3].

Antidiabetic agents have been shown to reduce levels of serum liver biomarkers [4], and cause serious side effects such as hypoglycemia, indigestion, edema, lactic acidosis, especially for those who are comorbid with heart failure or impaired liver function and kidney [5,6]. Herbs, because of the ease of access, has become an alternative medicine for people with diabetes mellitus in the community. In addition, the herb is also considered to be more effective, have low side effects and relatively low cost [7,8].

6 Many studies have shown that *Phyllanthus niruri* Linn has antidiabetic activity and alloxan which has been used to induce experimental diabetes due to the selective destruction of the insulin-producing pancreatic beta-islets [9,10,11]. However, those studies had only had limited data which were available on the possible association between activity of *phyllanthus niruri* linn with liver and renal serum marker enzymes and functions.

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### MATERIALS AND METHODS

2 This experiment was carried out in Department of Clinical Science, Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia during 2015.

#### Ethical approval

All the rats were handled based on the ethical principles for animal experiments and all the experiment procedure were approved by the research ethics committee of the university.

#### Chemicals

9 Alloxan was obtained from Sigma (St. Louis, MO, USA) and all other chemicals used were of analytical grade. *Phyllanthus niruri* was obtained from Xian Biof Biotechnology Gaoxin District of Xi'an, China.

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### Induction of Diabetes Mellitus

Male Wistar rats weighting from (180-200 g) were housed in standard conditions and fed with normal diet and water ad libitum. Diabetes was induced by intraperitoneal injection of alloxan (Sigma, St. Louis, Mo, USA) at a dose of 150 mg/kg body weight. Alloxan was dissolved in 0.9% sodium chloride. After the injection, they had free access of food and water. The rats were given 5% glucose solution after 6h. from alloxan injection to drink overnight to counter any hypoglycemic shock. The diabetic state was assessed by measuring the fasting plasma glucose concentration 72 h. after alloxan treatment in fasting rats. The rats with a plasma glucose level above 250 mg/dl were selected for the experiment and considered as diabetic [12].

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### Animal Treatment

Twenty five healthy male Wistar rats (about 180–200 g body weight) were obtained from Animal Experimental Laboratory, Faculty of Biochemistry, Universitas Airlangga. All animals were conditioned at room temperature at a natural photoperiod for 1 week before experiment execution. A commercial balanced diet and tap water ad libitum were provided. The duration of experiment was 4 weeks. The rats were randomly divided into 5 groups (5 rats each) as follows: Group 0 (G0), healthy control rats received distilled water as sole drinking source; Group 1 (G1), diabetic rats; Group 2 (G2), diabetic rats were treated with 1.35 mg phyllanthus niruri extract/day; Group 3 (G3), diabetic rats were treated with 2.7 mg phyllanthus niruri extract/day, and Group 4 (G4), diabetic rats were treated with 5.4 mg phyllanthus niruri extract/day orally.

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### Biochemical Factors Evaluation

At the end of experiment, rats were sacrificed under chloroform anesthesia and blood samples were collected by intracardiac puncture. The sera prepared through centrifuging at 3000 rpm for 15 minutes at 4°C. Serum biomarkers of liver function include alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Renal serum marker enzymes include blood urea nitrogen (BUN) and creatinine, were measured by using commercially available kits. Aminotransferases (ALT and AST) were measured to determine the concentration of intracellular hepatic enzymes that have leaked into the circulation and serve as a marker of hepatocyte injury. The increasing serum levels of blood urea nitrogen and creatinine, thereby indicate damage to kidneys.

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### Statistical Analysis

Data are presented as mean  $\pm$  SD and analyzed for statistical significance among group means by one way analysis of variance (ANOVA) followed by a post-hoc least square difference (LSD) for individual group comparison with the help of a software SPSS 7.5 for windows. The values were considered statistically significant when p-value was less than 0.05.

## RESULTS

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The effect of repeated oral administration of extract P. niruri on blood glucose is shown in Table 1. In normal control rats, blood glucose levels observed for 28 days after treatment indicate no significant difference with pre-treatment levels. In diabetic control rats there was constant increase in blood glucose for 28 days. However, administration of the most effective dose (5.4 mg/kg body weight) of the extract produced a hypoglycaemic effect. The level of glucose was almost similar to the normal control rats.

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**Table 1.** Effect of Phyllanthus niruri on blood glucose of diabetic rat

Treatment	Blood glucose Level (mg/dL)	
	Diabetic (Pre-treatment)	Diabetic (Post-treatment 14 Day)
G0	82.17 <sup>a</sup> $\pm$ 1.29	90.20 <sup>a</sup> $\pm$ 2.25
G1	328.45 <sup>c</sup> $\pm$ 48.32	350.20 <sup>c</sup> $\pm$ 50.10
G2	414.1 <sup>d</sup> $\pm$ 60.42	241.23 <sup>b</sup> $\pm$ 20.32
G3	324.01 <sup>c</sup> $\pm$ 55.07	112.31 <sup>ab</sup> $\pm$ 10.35
G4	330.21 <sup>b</sup> $\pm$ 48.2	98.00 <sup>a</sup> $\pm$ 15.7

Values are expressed as mean of five individuals in each group  $\pm$  SD.

Means with different superscripts letters are significant at  $p < 0.05$ .

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The effects of aqueous extract of P. niruri on the levels of pathophysiological marker enzymes ALP and ALT in serum of experimental rats have been depicted in Table 2. The levels were found to be

increased significantly (p<0.05) in alloxan-treated rats (G1) compared to control rats (G0). Upon treatment with *P. niruri* extract, the levels were brought back to near normalcy in G2, G3 and G4 group.

**Table 2.** Effects of alloxan and *Phyllanthus niruri* on the activities of ALT and AST enzymes in the serum of control and experimental animals

Serum constituent	G0	G1	G2	G3	G4
ALT (U/L)	46.60 <sup>a</sup> ±14.60	155.00 <sup>b</sup> ±16.23	76.60 <sup>a</sup> ±62.66	50.00 <sup>a</sup> ±8.90	58.00 <sup>a</sup> ±19.17
AST (U/L)	88.40 <sup>a</sup> ±12.44	215.60 <sup>b</sup> ±24.08	109.40 <sup>a</sup> ±11.39	89.20 <sup>a</sup> ±10.69	97.20 <sup>a</sup> ±18.39

\* p<0.05 between normal and diabetic control and between diabetic control and diabetic with fenugreek alkaloid extract

\* p<0.05 between normal and diabetic control and between diabetic control and diabetic with fenugreek alkaloid extract

Values are expressed as mean of five individuals in each group ± SD.

Means with different superscripts letters are significant at p<0.05.

Table 3. shows the effect of aqueous extract of *P. niruri* on the circulating blood urea nitrogen and serum creatinine concentrations in alloxan induced diabetic rats. Oral administration of 150 mg/kg alloxan for 4 days was associated with significant elevation in the circulating levels of blood urea nitrogen and serum creatinine in G1 rats after 28 days (p<0.05). Treatment with *P. niruri* attenuated significantly the changes in the serum levels of blood urea nitrogen and creatinine in G2, G3 and G4 groups (p<0.05).

**Table 3.** Effects of alloxan and *Phyllanthus niruri* on the levels of blood urea nitrogen (BUN) and creatinine of control and experimental animals

Serum constituent	G0	G1	G2	G3	G4
BUN (mg/dL)	15.00 <sup>a</sup> ±3.92	45.00 <sup>b</sup> ±4.85	23.90 <sup>a</sup> ±7.96	16.90 <sup>a</sup> ±10.26	24.00 <sup>a</sup> ±13.66
Creatinin (mg/dL)	0.44 <sup>a</sup> ±0.10	2.37 <sup>b</sup> ±0.46	0.41 <sup>a</sup> ±0.07	0.44 <sup>a</sup> ±0.05	0.45 <sup>a</sup> ±0.07

Values are expressed as mean of five individuals in each group ± SD.

Means with different superscripts letters are significant at p<0.05.

## DISCUSSION

Liver enzymes such as AST and ALP are marker enzymes for liver function and integrity [13]. In this study, increased activities of AST and ALT were observed in the diabetic animals. Hence it indicates that diabetes may induce hepatic dysfunction in rat. The increase in the level of these enzymes in diabetes may be as a result of leakage from the tissues and migration into the bloodstream [14]. Diabetic patients may have damage to various tissues. The damage can increase serum level of ALT and AST. Levels of ALT may rise sharply if there is injury to hepatocytes, cardiac muscle, striated muscle, pancreas, kidney and erythrocytes. Serum level of AST will increase when hepatocytes, cardiac muscle, striated muscle, and pancreas have damage [15].

Administration of *P. niruri* extract can reduce AST and ALT. This showed that *P. niruri* has a protective effect on the liver damage in diabetic rats. *P. niruri* contains hypophyllanthin and phyllanthin which are anti-hepatotoxic activities [16]. Phyllanthin and hypophyllanthin can provide hepatoprotective effects on the liver because they have antioxidant activity [17]. The content of this antioxidant protects liver tissue from oxidative damage and helps liver cell regeneration [18]. Antioxidants also have membrane stabilizing activity of the liver cells which will reduce liver damage [19].

In addition to being anti-oxidants, *P. niruri* is also proven to have anti-inflammatory activity. In this case, *P. niruri* acts as a vasoconstrictor caused by inflammation. How it works is by blocking nitrite oxide (NO) and prostaglandine E-2 (PG E2), lowering induced nitric oxide synthase (iNOS), cyclooxygenase-2 (COX 2) and inhibiting the production of NF-κB. In addition, *P. niruri* also decrease the expression of interleukin-1β, interleukin 10, interferon-γ and tumor necrosis factor-α [20].

The main function of the kidneys is to excrete the waste products of metabolism and to regulate the body concentration of water and salt. Significant increase of total urea and creatinine levels indicated impaired renal function of diabetic rats which led to a negative nitrogen balance, enhanced proteolysis and lowered protein synthesis [21,22]. Similar results are observed in the earlier studies by using different plants [23]. The improvement of renal biochemical functions with *P. niruri* in the present investigation could be due to its antidiabetic action, which results in alleviation of altered metabolic status in animals and by the regenerative capability of the renal tubules [24].



## CONCLUSION

The present study demonstrated clearly that *Phyllanthus niruri* extract showed the hypoglycemic effect. In addition, the extract can protect liver and renal function in alloxan induced diabetic rats directly, or indirectly through a reduction of blood glucose level. Further research on isolation of compound and the molecular analysis about these effects are required to understand the mechanism.

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## COMPETING INTEREST

The authors declare that they have no competing interest.

## AUTHORS' CONTRIBUTION

WMY carried out the main research works, performed the statistical analysis and analyzed the main data in the experiments. BSL helped to draft the manuscript. All authors read and approved the final manuscript.

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